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Hyperurikaemie - nur Gicht oder auch kardio-renales Risiko ?

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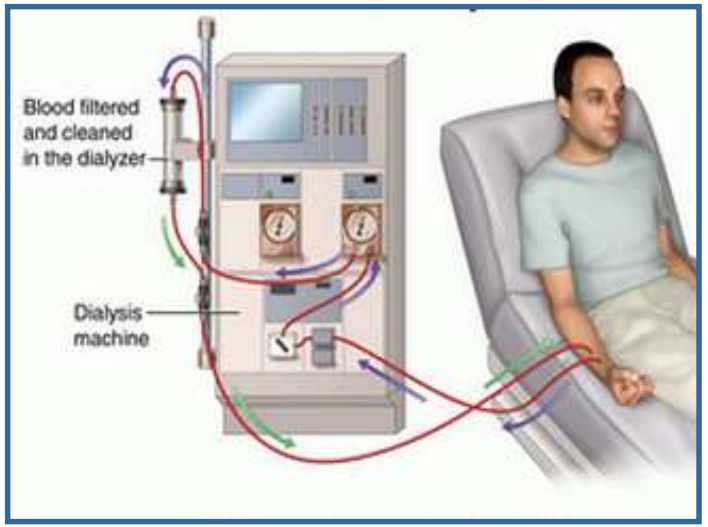
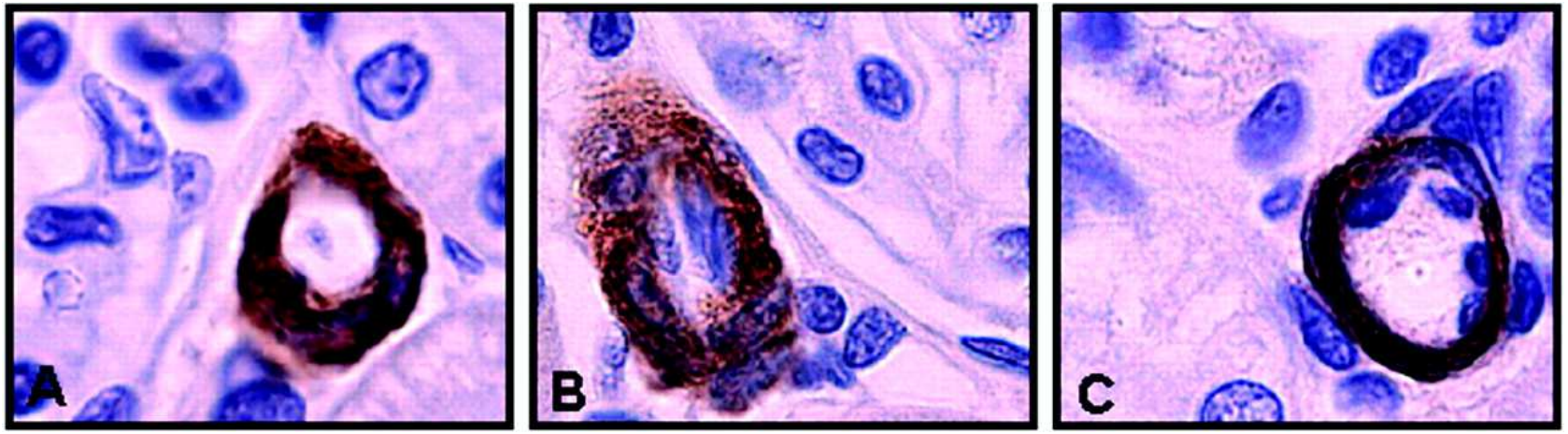
Hyperurikamie - das Zipperlein !



Hyperuricemia & cardio-renal risk

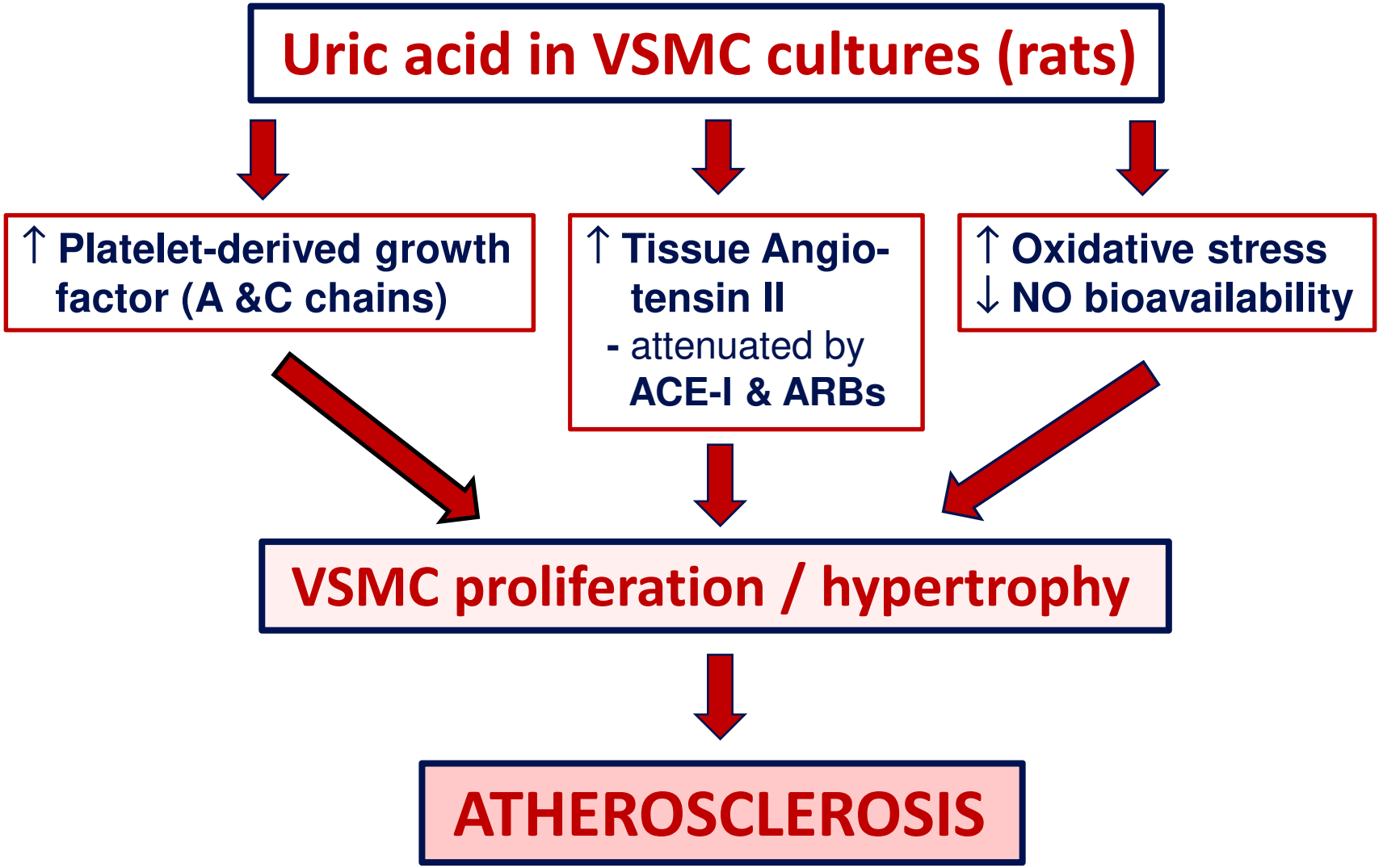
Animal experiments: male **Sprague Dawley rats** fed **2% oxonic acid** (OA) on **low salt diet** (LS) → **mild hyperuricemia** → kidney biopsies after 5 weeks: **afferent glomerular arterioles**



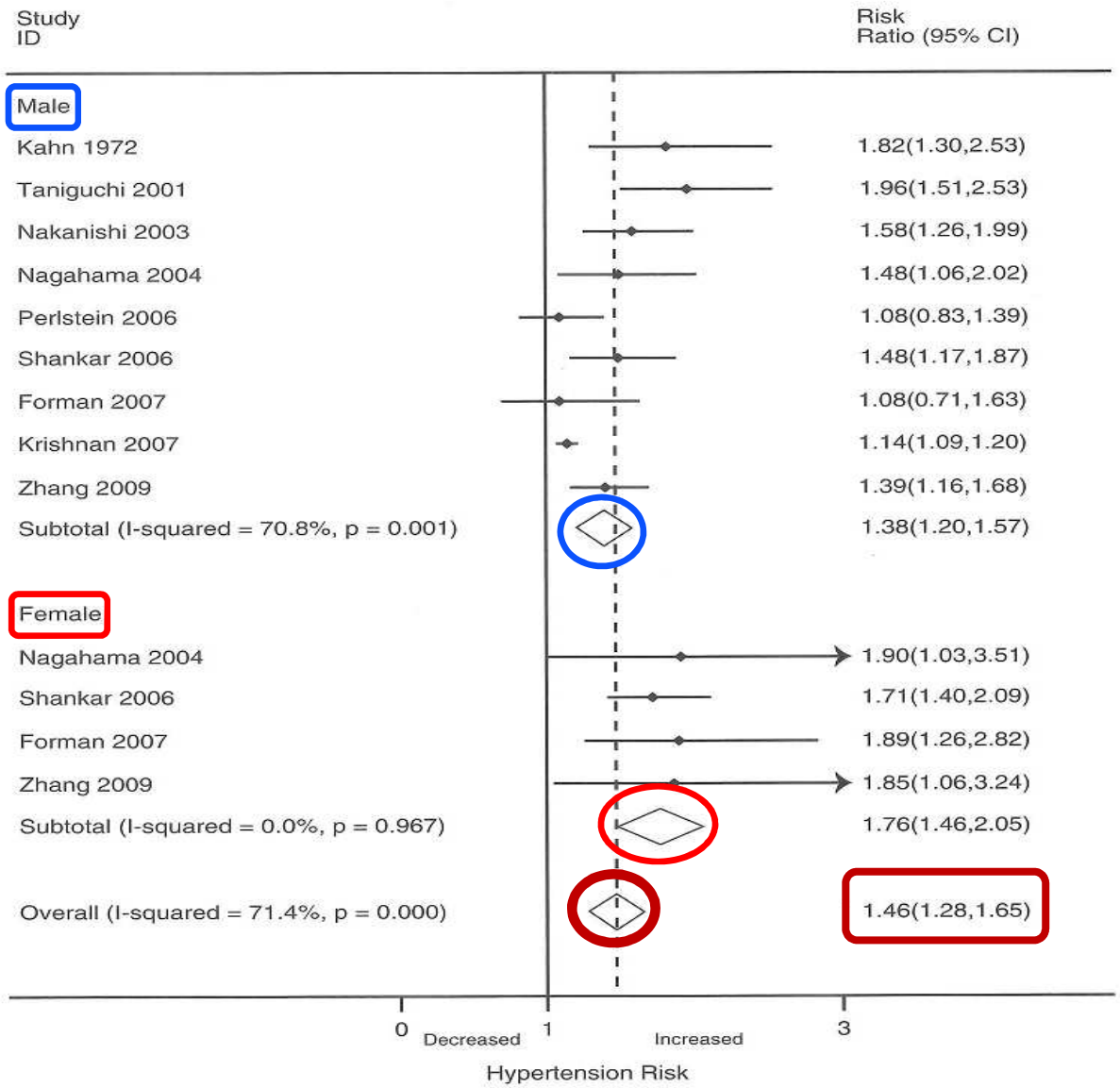
LS (control)	LS/OA	LS/OA & Allopurinol
P_{GC} 51.9	56.7	50.1 mmHg
sBP 126.4	143.3	121.8 mmHg

⇒ **systemic/intrarenal hypertension & glom. arteriolopathy** in hyperuricemic animals, **abolished by allopurinol**

Rats - hyperuricemia & atherosclerosis



Hyperuricemia and hypertension



Meta-Analysis :

- 18 prospective cohort studies
- 55'607 subjects
- endpoint: incident hypertension

(Grayson PC et al. Arthritis Care Res 63: 102-110, 2011)

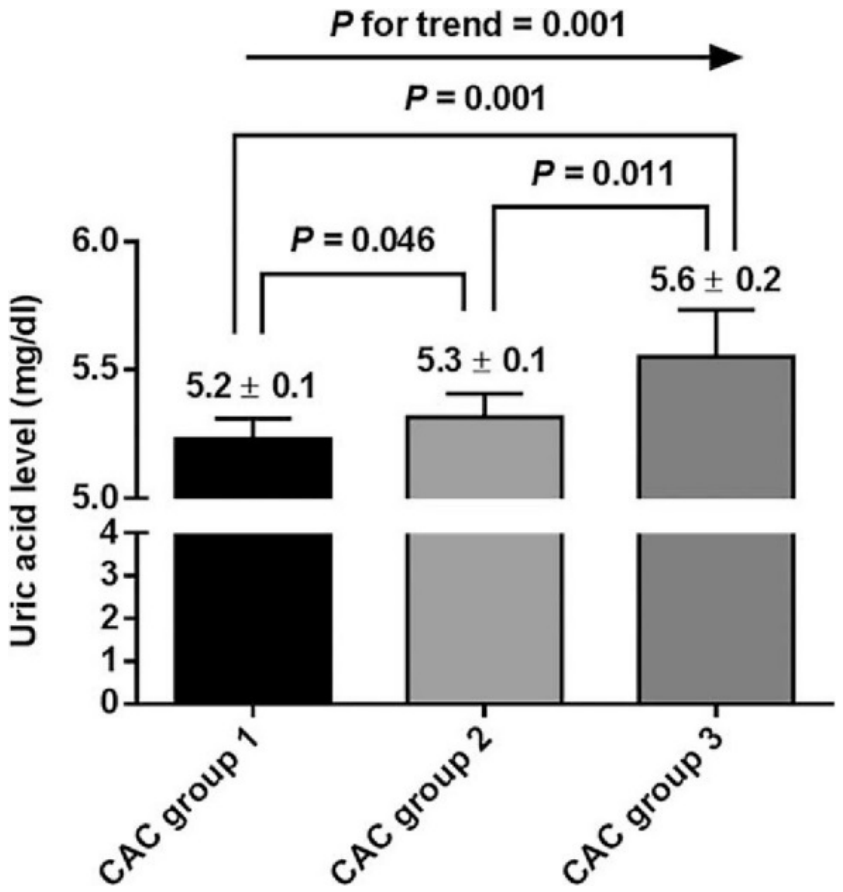
Hyperuricemia & coronary artery calcification

Cross-sectional retrospective study 2006-2013 :
Check-up in **4884 South Koreans**, **excluded:** <20/>80 years, CAD, gout, nephro-lithiasis, medications altering S-UA ⇒ **4188 subjects** (2559 males, 1629 females)

Multidetector computed tomography
(3 mm slices, reconstruction interval 1.5 mm)
→ **coronary artery calcium (CAC) scores**

- **CAC group 1**: CAC score **0 = calcium absent**
- **CAC group 2**: CAC score **1-299**
- **CAC group 3**: CAC score **≥ 300**

Multivariate-adjusted associations between **S-uric acid and CAC scores** (adjusted for age, sex, diabetes mellitus, hypertension, smoking, sBP, BMI, CRP, Hb, WBC, eGFR, glucose, lipids)



 (from Kim H et al., Medicine 2017 Apr; 96(14):e6565. doi: 10.1097/MD.0000000000006565

Hyperuricemia and CV disease - allo-purinol in hypertensive adolescents

30 adolescents (11-17 yrs.), never-treated **stage 1 hypertension, S-uric acid > 356 µmol/l. Randomization :** Allopurinol 2 x 200 mg/d vs. placebo **4 weeks**

Parameter	Mean (95% Confidence Interval)		*P* Value
	Placebo	Allopurinol	
Change in casual systolic BP, mm Hg	–2.0 (0.3 to –4.3)	–6.9 (–4.5 to –9.3)	.009[a]
Change in casual diastolic BP, mm Hg	–2.4 (0.2 to –4.1)	–5.1 (–2.5 to –7.8)	.05

Table 3. Effect of Placebo and Allopurinol on Non–Blood Pressure End Points

Parameter	Mean (95% Confidence Interval)			*P* Value
	Pretreatment[a]	Placebo	Allopurinol	
Heart rate, beats/min	72 (67-78)	74 (69-80)	75 (69-80)	.87
Cardiac output, L/min	6.4 (5.6-7.1)	6.2 (5.4-7.0)	6.6 (5.9-7.2)	.56
Systemic vascular resistance index, (dyne s/cm^5)/m^2	2478 (2223-2731)	2473 (2232-2615)	2136 (2056-2228)	.03[b]
Total body water, L	27.8 (26.0-29.7)	28.0 (26.1-30.1)	28.1 (26.0-29.9)	.86
Plasma renin activity, ng/mL/h	1.9 (1.7-2.2)	2.1 (1.8-2.4)	1.4 (0.8-2.1)	.02[b]

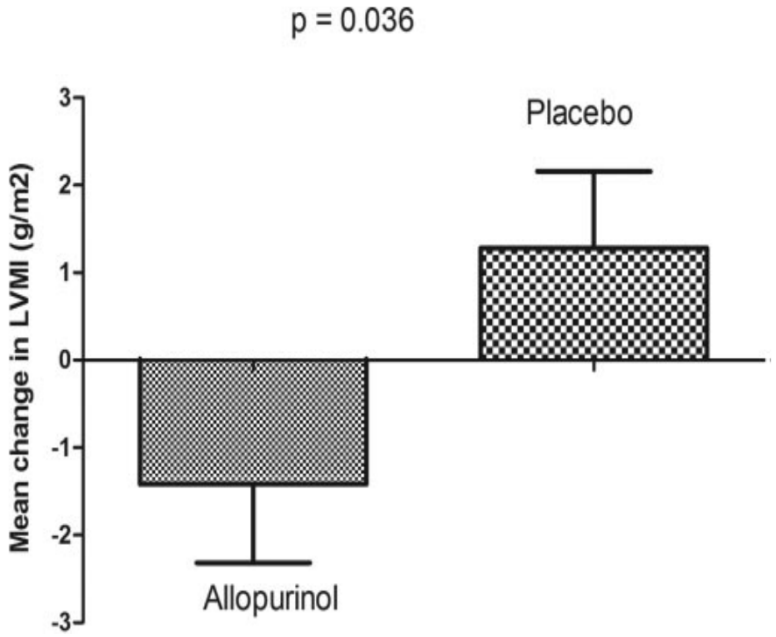
[a] Pretreatment values were measured prior to first treatment phase.
[b] Exploratory end points.

Hyperuricemia & CV disease - Allopurinol effects on LV mass & endothelial dysfunction in CKD - RCT

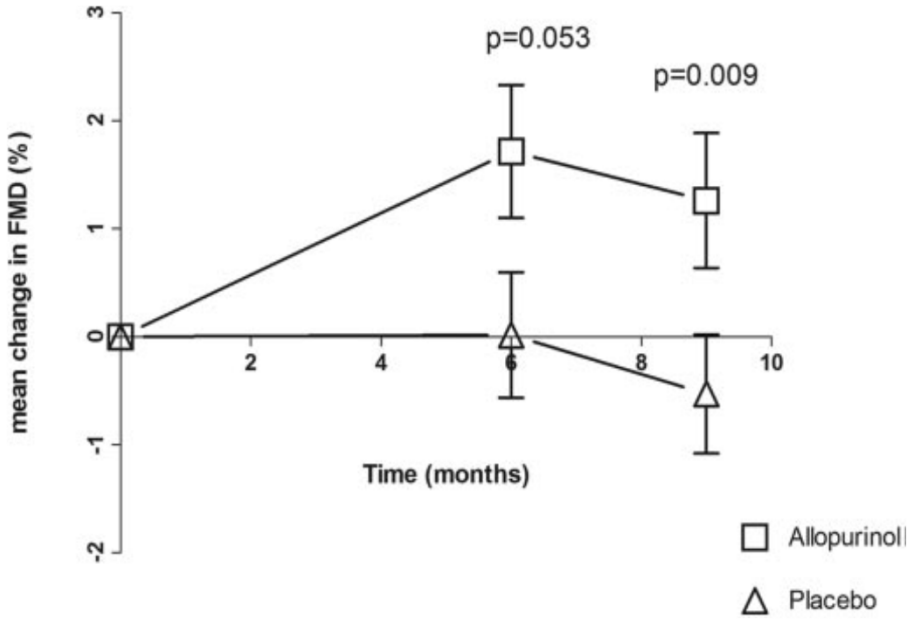
67 elderly patients, CKD stage 3, LV hypertrophy, randomization: allopurinol 300 mg/d *vs.* placebo on top of other medication (not different between groups), **9 months, 53 finished study** (27 A, 26 P). **NO difference in sBP & dBP** at 9 months.

ΔS-UA : Allopurinol 440 to **260 µmol/l**, Placebo 420 to **440 µmol/l** ($p < 0.0001$)

Left ventricular mass index



Flow-mediated dilation brachial artery



Uric acid lowering: effects on Renin-Angiotensin-system and ambulatory blood pressure - RCT

Double-blind placebo-controlled trial 2011-2015

- **149 adults**, **BMI ≥ 25 kg/m²**, mean **serum UA 6.1 mg/dL** (363 µmol/l)
- 62% white, male/female 1 : 1
- **Excluded**: hypertension, CAD, eGFR < 60, malignancy, liver disease
- **Randomization** : 8 weeks treatment with
  - Placebo (n = 53, 45 completed study)
  - Allopurinol (n =49, 35 completed study)
  - Probenecid (n = 47, 40 completed study)

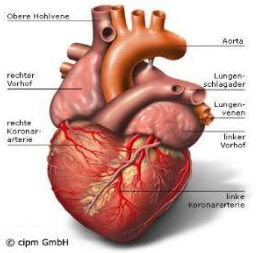
Primary endpoints : systemic and kidney-specific RAS-activity

- **NO differences between groups** despite significant uric acid lowering in both treatment arms *vs.* placebo
- **NO changes** in **plasma renin and angiotensin II**

Secondary endpoints : mean 24h-BP, awake/asleep BP, night dipping

- **NO changes, NO differences between groups**

Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART study



Multicentre, controlled, prospective, randomised, open-label blinded end point (PROBE) trial of **allopurinol (up to 600 mg daily) versus no treatment** in a 1:1 ratio, **added to usual care**, in **5215 patients aged 60 years and over** with **ischemic heart disease** (Scotland & GB).

The **primary outcome** is the **composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.**

The study is event-driven and results are expected after 2019.

SUMMARY - Hyperuricemia & CV disease

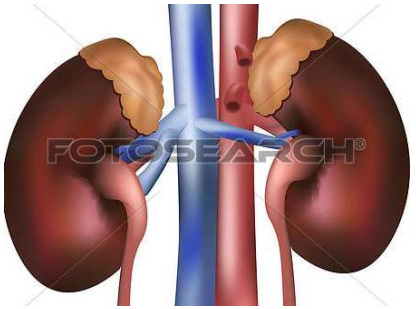
There is clinical evidence that hyperuricemia….

- **… increases BP / induces systemic arterial hypertension in adolescents, but *not in adults* (different pathophysiology ?)**
- **… is associated with coronary artery calcification**
- **… causes vascular hypertrophy / endothelial dysfunction** (reduced flow-mediated dilation)
- **… modestly increases left ventricular mass index**

Xanthine oxidase inhibition…

- **… is able to reduce blood pressure in *adolescents***
- **… can attenuate endothelial dysfunction** in adolescents and adults
- **… is able to reduce LV mass index in elderly adults**

Hyperuricemia & chronic kidney disease - epidemiology



Vienna Health Screening Project, 21'475 healthy volunteers, mean follow-up **7.4 years, 73'015 follow-up examinations, eGFR** calculated by MDRD formula

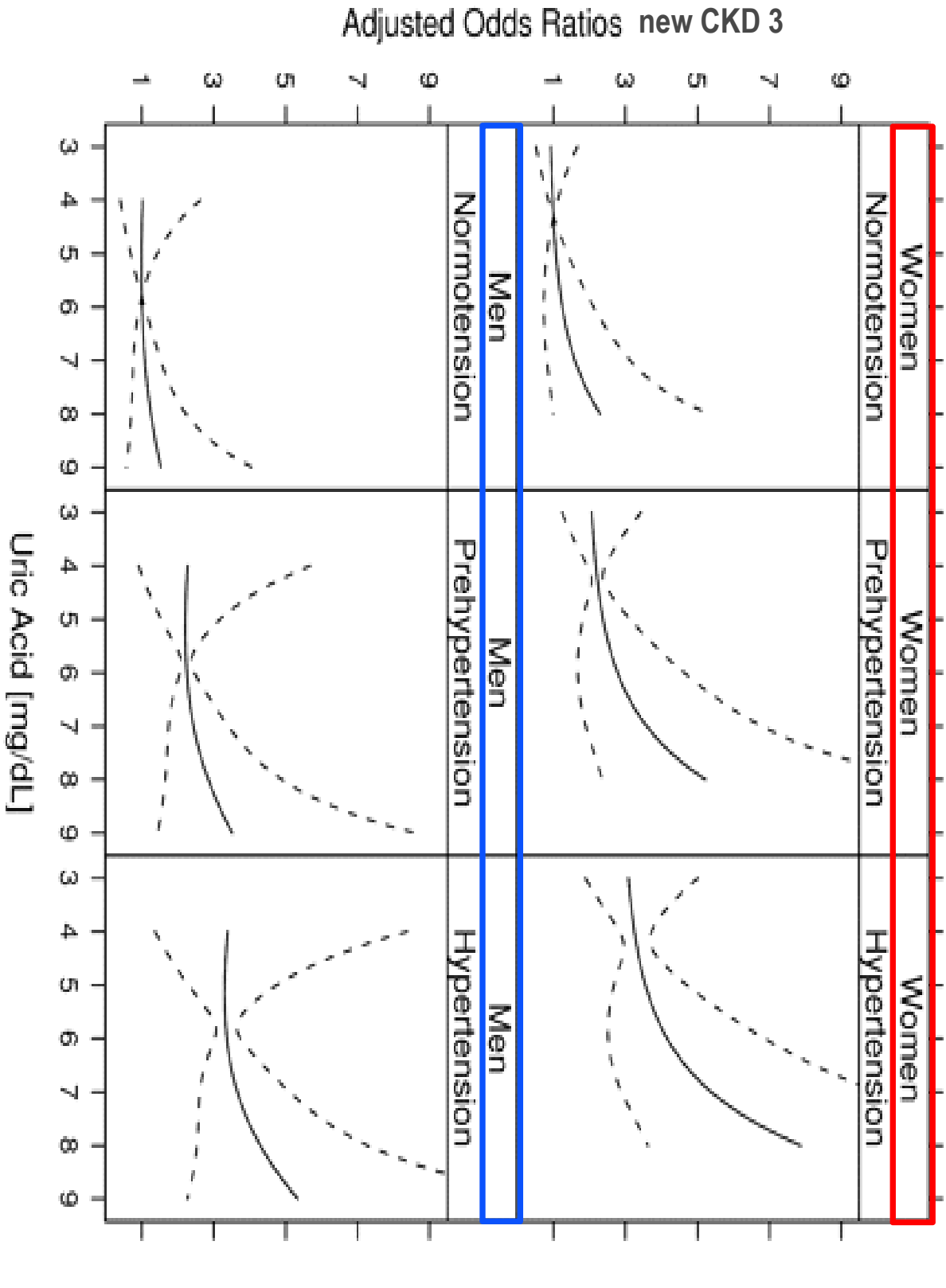
Statistics :

Adjustments for age, gender, waist circumference, mean arterial BP, antihypertensives, blood glucose, blood lipids, baseline eGFR

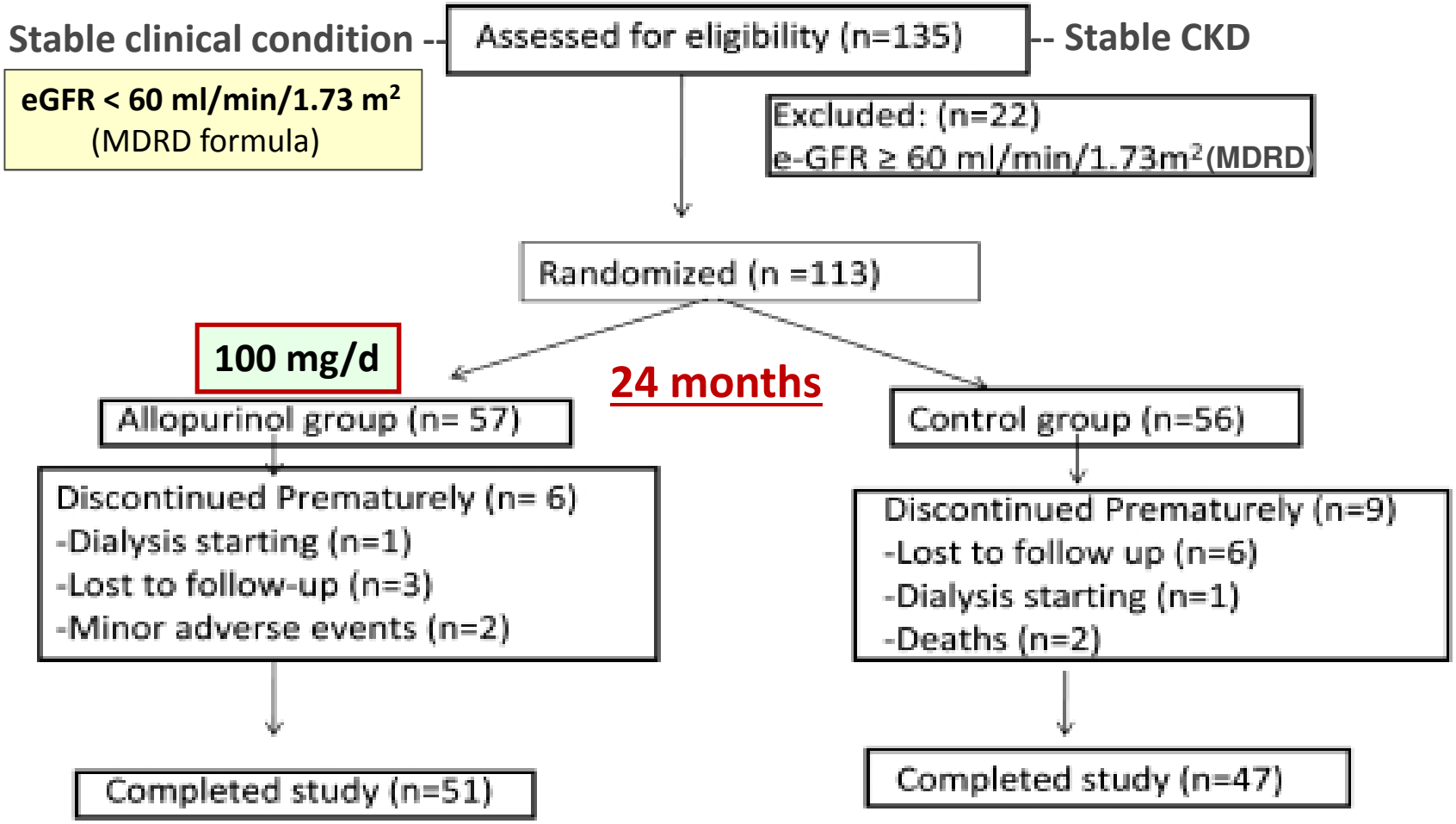
Primary outcome/results : development of CKD stage 3 (eGFR < 60) in relation to **serum uric acid (S-UA) at baseline** :

- **Normal reference**: S-UA < 7.0 mg/dl (**< 416 µmol/l**) OR 1.00
- **Sligthly elevated:** S-UA 7.0 – 8.9 mg/dl (**416-529 µmol/l**) **OR 1.74**
- **Elevated** : S-UA ≥ 9.0 mg/dl (**≥ 530 µmol/l**) **OR 3.12**

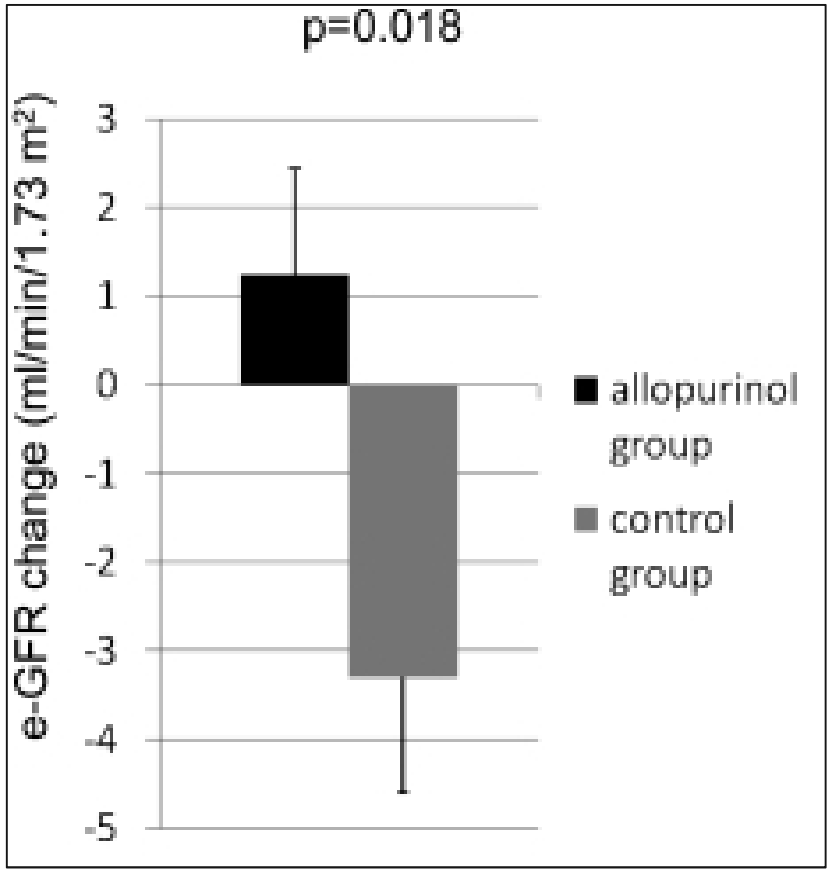
Hyperuricemia & chronic kidney disease (2)

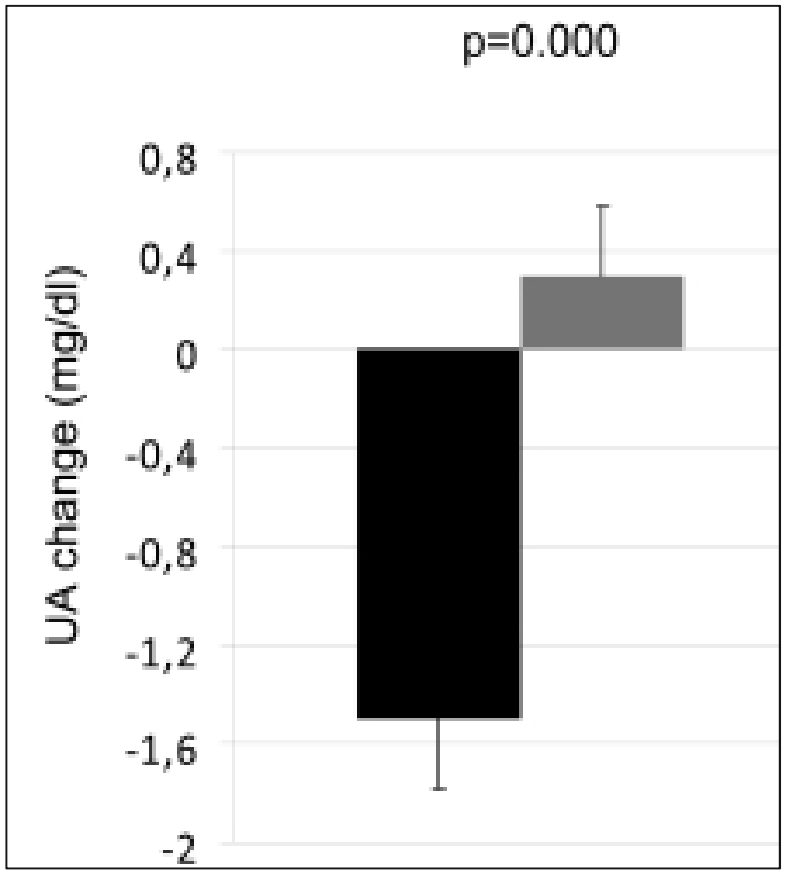


Allopurinol & chronic kidney disease - randomized evidence

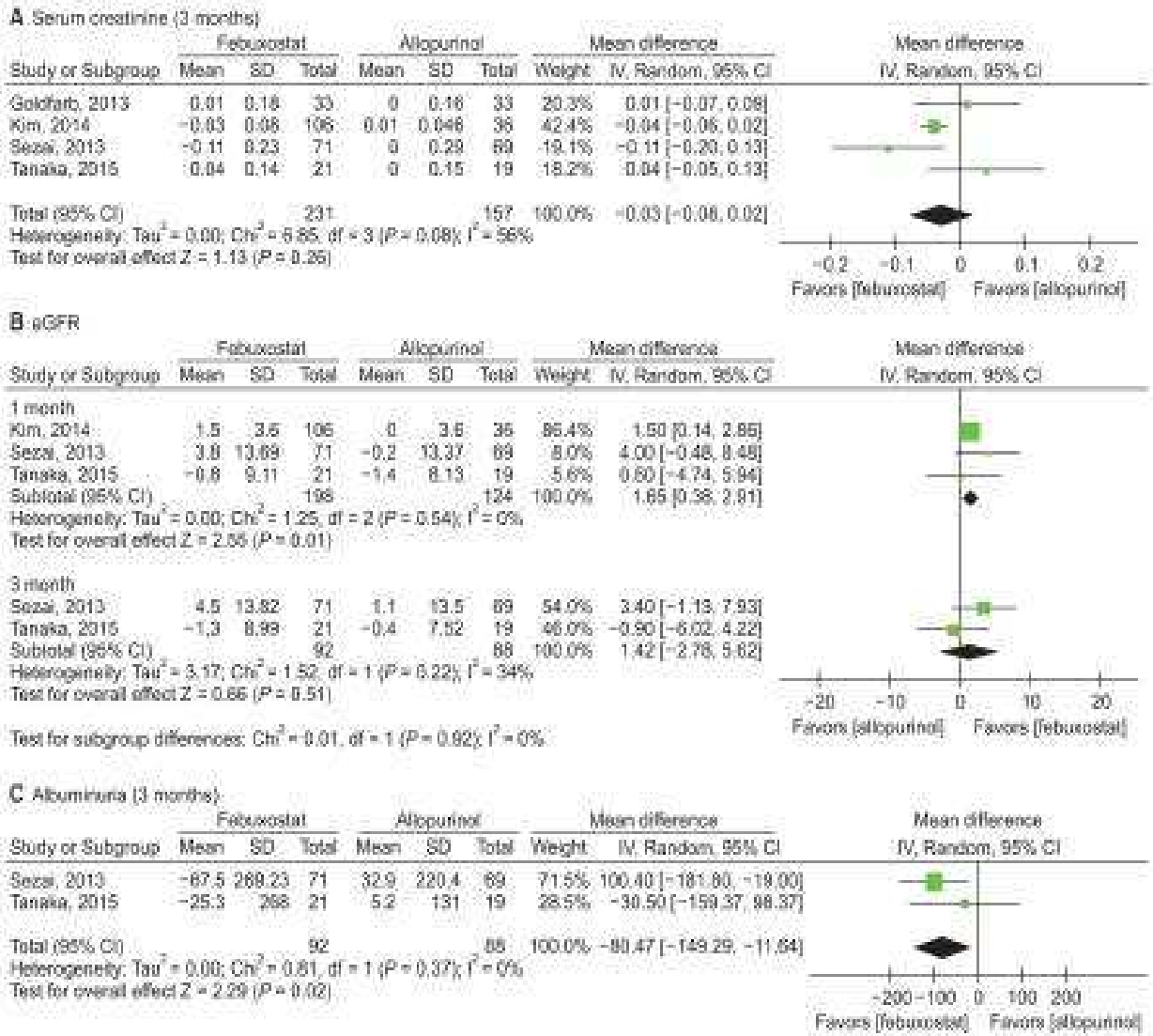


Allopurinol & chronic kidney disease - randomized evidence (2)





Renoprotection - allopurinol vs. febuxostat



Literature search

- **49 full-text articles**
- **45 excluded** (no RCTs, conference papers, no adequate outcome, duplication)

Meta-analysis

- **4 RCTs included**
- **Endpoints :**
  - S-creatinine
  - eGFR
  - Albuminuria
  - S-uric acid

Allopurinol & chronic kidney disease - the „field“ evidence

Retrospective cohort study :

Medicare data 2006-2012 (U.S.), 5% random sample, age ≥ 65 years, newly treated with allopurinol (e.g. filled allopurinol prescription after 183 days without prescription)

Main outcome : 1st occurrence of **renal failure** (ICD-9) during follow-up

Predictors : allopurinol **dose**, **duration** of allopurinol use

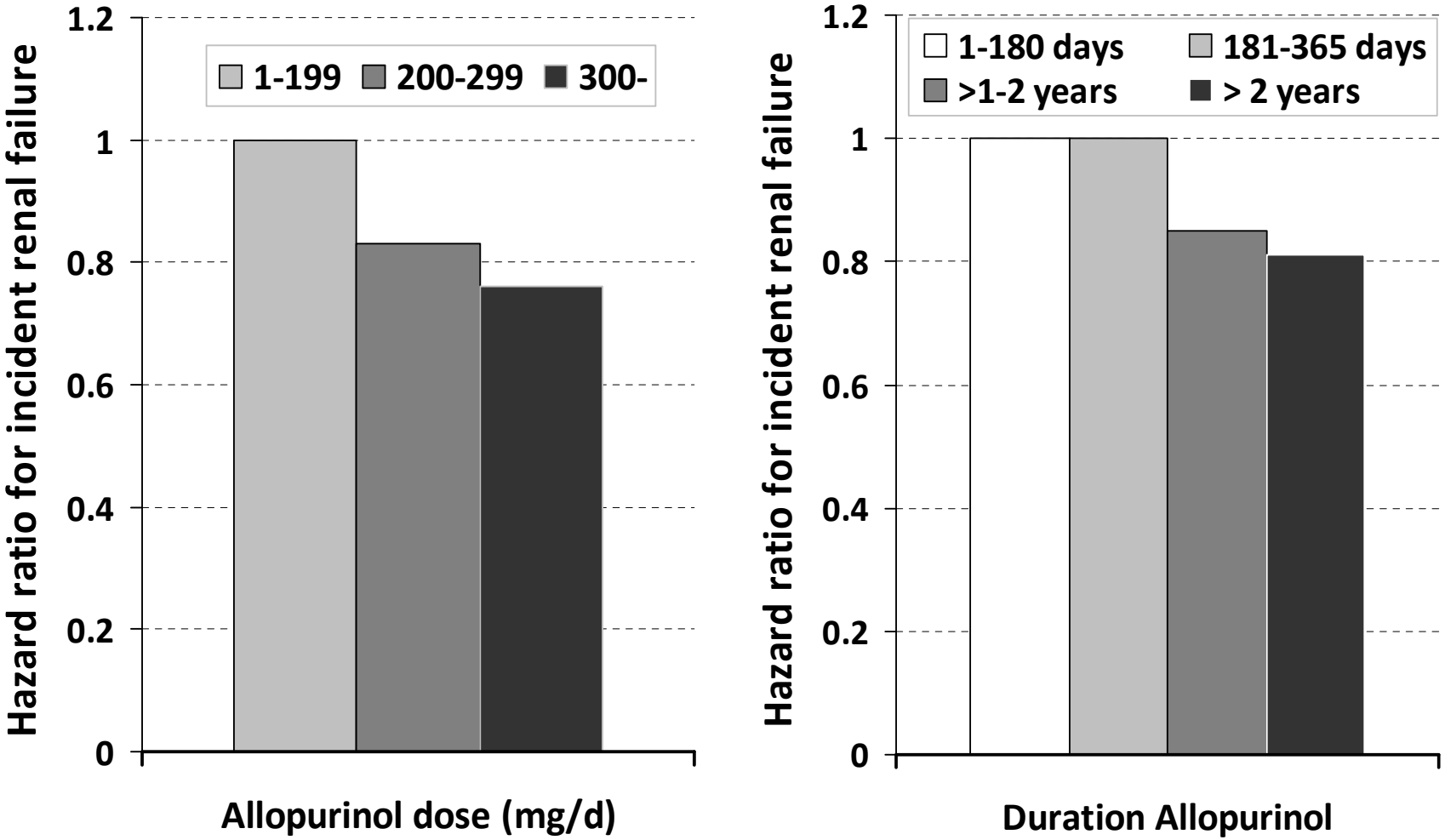
Multivariate adjustments :

- age, gender, race, Charlson-Romano comorbidity index
- Medications: β–blockers, ACE inhibitors, statins, diuretics, allopurinol

Cohort characteristics :

- **30’022 allopurinol treatments** without history of renal failure (baseline)
- **Follow-up**: 8314 episodes with incident renal failure, 21’708 without

Allopurinol & chronic kidney disease - the „field“ evidence (2)



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KONKLUSIONEN

1. **Hyperurikaemie** ist nicht einfach Gicht…

2. **Evidenz** (exp./klin. Studien) für **Hyperurikaemie** als...

   …CV Risikofaktor : Endothelschaden/-dysfunktion, VSMC Proliferation, ↑ BD und ↑ Renin bei Adoleszenten, LVH bei älteren Erwachsenen

   ABER: nur kleine Studien, *grosse randomisierte, placebo-kontrollierte Studien fehlen*

   …renaler Risikofaktor: gute epidemiologische Evidenz, Harnsäure-Effekt durch Hypertonie verstärkt

   ABER: *grosse randomisierte, placebo-kontrollierte Studien fehlen*

3. **Harnsäuresenkung mit Xanthinoxidase-Hemmern**…

   …kann CV und renales Risiko senken, unabhängig von andern RF

   …zeigt in **höheren Dosen** und über **längere Therapiedauer** whs. **mehr Benefit, *ABER* : *keine*** *randomisierte, placebo-kontrollierte Studien*